REMARKS

Claims 5-11 are active and are drawn to the elected subject matter.

The invention as defined in Claim 5 is

A method for treating Alzheimers Disease (AD) in a patient in need of such treatment, the method comprising

contacting blood or plasma flow of a patient suffering from AD or a patient with a risk for AD with an apheresis device, the apheresis device comprising a solid carrier, said solid carrier having anti-amyloid-β precursor protein (APP) antibodies attached to a surface of the solid carrier, and wherein contacting with the apheresis device is for a time sufficient to reduce APP polypeptides in the brain and treat AD in the patient.

The Examiner has maintained the rejections applied under 35 USC 103(a) citing to DeMattos and Kojima and further in view of Boos is requested. Applicants continue to respectfully disagree and provide a Rule 132 Declaration from an expert in the field of neurodegenerative diseases and supportive publications that establish that the rejections cannot be sustained.

As explained by Dr. Masliah, one in this field would not have thought to do what is defined in the claims of this application based on the publications of DeMattos and Kojima.

The USPTO misinterpreted some of the data and results of the DeMattos paper and did not take into consideration the difference between an antibody which is administered to a patient and acts intra-corporally and an antibody which acts via immobilization on the solid surface extra-corporally as in the claims of this application.

First, the USPTO refers to a "peripheral" administration of m266 and from this I can only infer that the USPTO views that m266 antibody exclusively acts from the periphery (the blood) and does not even occur in the brain or in the CSF. However, this is not true. Even in

the DeMattos et al, it is clear that m266 also crosses the blood brain barrier (BBB); the separation of circulating blood and cerebrospinal fluid (CSF) in the central nervous system (CNS); occurring along all capillaries and consisting of tight junctions around the capillaries that do not exist in normal circulation. DeMattos stated on page 8852, right column, that the concentration of the antibody in CSF was 12.0 ± 0.95 ng/ml. Despite the fact that in DeMattos it was speculated that this amount "should only be able to account for an increase of Aβ of less than 1 ng/ml", the DeMattos statement turned out to be rather due to a detectability problem because in a follow-up publication (see enclosed article of Dodart et al. (Nature Neuroscience 5 (5) (2002): 452- 457) the same group found that the presence of the m266 antibody in the brain was important for reversing memory deficits in an Alzheimer's disease model. It is further shown that m266 can be detected in the brain in the high-dose groups whereas plasma increase is detected in all groups. Fig. 4D of Dodart et al. again showed that there is direct evidence for the presence ofm266 in the brain. This is also confirmed in the second paragraph on page 455, left column of Dodart et al., where it is stated that the antibody/Aß complex was also found in CSF at the lowest dose found to be effective in reversing learning and memory impairment . This again shows that besides the detectability problem this group had -the failure to detect m266 does not mean that there is no antibody present) - one would see the action of a peripherally administered anti Aβ antibody such as m266 (or of two additional examples: m3D6 and m10D5 also mentioned in DeMattos, left column, third paragraph, last sentence) as being able to cross the BBB and have a direct effect on Aβ/Aβ deposits in the brain.

It is therefore clear that, in contrast to the interpretation of the USPTO, administration of the m266 antibody is not connected to an exclusively peripheral effect but that this antibody is present in the brain and its extra-cellular compartment (in the CSF) *in vivo* following peripheral administration. Indeed, other antibodies for which crossing of the BBB

is known [see Kotilinek et al (J. Neuroscience 22 (2002), 6331-6335), Bard et al. (Nat. Med. 6 (2000), 916-.919), and, Hokoshi et al. (BBRC 325 (2004), 384-387] exert effects in the brain.

It is also known that an antibody in the CNS can foster the release of Aβ from the CNS significantly (see DeMattos., page 8852; and the attached Kotilinek et al, Bard et al, Hokoshi et al and Wilcox et al. (J. Neuroscience 23 (2003), 3745-3751) showing the crossing of peripherally administered anti-Abeta-antibodies over the BBB and the presence and functionality of such antibodies in the CSF/brain). Accordingly, the finding of DeMattos is not teaching that peripheral presence of an Aβ antibody (an APP antibody; i.e. an amyloid binding agent) is the basis for the effects observed *in vivo*.

Moreover, it has to be acknowledged that the velocity of Aβ release into the plasma is, in principle, also based on the enhanced presence of high affinity binders in the CNS following application. It is well known to the expert in the field that antibodies to CNS proteins reach the brain very fast after peripheral application (one hour or less) and can thus exert their function *in situ* very early after administration. See the attached publications of Freund (J. Exp. Med. 51 (1930), 889-902) and Masliah et al. (Neuron 46 (2005), 857-868).

To interpret the data contained in DeMattos, one would also have to include the extra-neuronal sources of Aβ which are present in the periphery of AD patients (as well as in the transgenic animals in the DeMattos study).

The blood and its cellular components are an important source for amyloid peptides. Platelets are well-known to constitute one of the major sources of Aβ in the blood. The antibody presence in the blood can thus also lead to a dramatic release from Aβ from the platelets into the bloodstream accounting at least, in part, for the increase of Aβ reported by DeMattos. Accordingly, the direct contact of high antibody levels with platelets is how the data presented by DeMattos can be reasonably interpreted.

In addition it is known that the highly abundant plasma protein albumin is capable of binding the amyloid peptide and is consequently usually associated with Aß peptides in the circulation. In fact, almost 90% of amyloid peptides in plasma are bound to albumin (see attached article of Biere et al., JBC 271 (1996), 32916-32922).

The USPTO on page 5, 2nd paragraph of the Official Action dated May 19, 2010 stated that "the ability to bring Aβ across the membrane is unique to this antibody and it can pull Aβ out of the brain. " However, this conclusion is not correct, and even if it was correct this still does not suggest to one in this field to do what is defined by the method of claim 1 with a reasonable expectation of success.

First, DeMattos clearly reports that the effect according to Fig. la is also present for other antibodies including m3D6 and m10D5 (see page 8851, left column, 3rd paragraph, last sentence). Moreover, a small amount of the antibody in the brain is sufficient to reduce the very lowly concentrated toxic Aβ species at synapses responsible for disturbing memory formation as described by the article of Dodart et al. (the same group that published DeMattos). As monoclonal antibodies are known to cross the BBB, albeit in low amounts of about 1 to 5%, even this amount is sufficient to clear amyloid deposits during chronic treatment. Moreover, cognitive benefits are detectable before amyloid reduction is detectable in the brain in the model used. This shows that even for DeMattos, one would understand that the effects reported by DeMattos relate to an effect of the antibody in the brain as being important for the overall results.

Even if it is true that Fig. 1 A would imply to a person skilled in the art that apheresis with an anti-Aβ antibody would decrease the concentration in the compartment on the other side of the membrane, in the case of the apheresis according to this application, this other side of the membrane would be the human blood and not the human brain. Moreover, it was not shown by DeMattos that the mere reduction of plasma level of Aβ was then sufficient to

reduce Aβ in the brain. This is an oversimplification artificially pulled out from this article by the USPTO with the knowledge of having read this application because I certainly do not come to that conclusion when reading DeMattos. In fact, in 2001, DeMattos with the knowledge of the subsequent work of this group, see again Dodart et al, one in this field would know that in addition to the known effects that administration of an antibody in the blood system has in the clearance of the compound to which this antibody binds (i.e. to Aβ) this antibody also exerts direct effects in the brain. This was regarded as essential for the effect of the administration of this antibody to the mouse model. Although being administered to the periphery, the antibody evidently crosses the BBB and has effects there which were decisive for the overall effect reported (see Dodart et al. 2002).

Kojima shows that an increased plasma level of p2-MG can be reduced in hemodialysis patients (see table 1 of Kojima). However, this reduced level in HD patients is still significantly higher than normal levels (see also table 1 of Kojima). IgE or SAP levels in plasma are shown to be decreased by applying the method. However, Kojima does not contain any information that amyloid depositions in certain compartments or even in the brain decrease with this method. Even if Kojima had shown reduction of several amyloid depositions, this would still only be a reduction within the blood system, i.e., in the periphery.

Claim 1 of the present application fundamentally differs from Kojima's approach, because apheresis is applied to the blood or plasma flow to reduce amyloid deposition, including APP, in the brain (and not in plasma). Plasma of AD patients does not show an elevated Aβ level. Quite in contrast, DeMattos shows a rapid 1000-fold increase in plasma Aβ. Even though, a corresponding β2-MG antibody has not been tested in Kojima, it would be expected that such rapid increase in β2-MG does not occur, because the biology of the proteins in Kojima differs so fundamentally from Aβ used in the context of this application.

It is clear that DeMattos differs fundamentally from the manner and goal that claim 1 of this application sets out to treat AD and the addition of Kojima simply is not combinable with DeMattos. Even if one did combine those references, there would not have been a reasonable expectation of success due in large part to the significant and fundamental differences between β2-MG as taught in Kojima compared to the Aβ in the claims of this application.

Reference is again made to Boos et al. disclosing a specific apheresis device but does not compensate for the fact that the combination of DeMattos and Kojima are not combinable and even in combination fail to teach the claimed invention with a reasonable expectation of success as required under the law.

Reconsideration and withdrawal of the rejections is requested.

To the provisional rejection citing copending application 11/571,970, in accordance with MPEP § 822.01, Applicants request that if the "provisional" double patenting rejection in the present application is the only rejection remaining, the examiner should then withdraw that rejection and permit the present application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent, if applicable.

Allowance of the claims is requested.

Respectfully submitted,

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